- from 10 to 60% by weight of hydroxypropyl methyl cellulose based on ethyl cellulose; and
- from 0.1 to 40% by weight of silica with antistatic and permeabilizing properties, based on ethyl cellulose.

Thanks to said specific composition of the mixture constituting the coating, said particles of ibuprofen microcrystals allow:

taste masking of ibuprofen,

significantly reduced irritant effect of ibuprofen on the throat,

preservation of ibuprofen physico-chemical integrity and substantially immediate release of the ibuprofen.

The Examiner considers that Carli et al. and Dunn et al. *"provide the theory to the coating of granulated ibuprofen with cellulose derivatives and silica products".*

Further he adds that the ranges and concentrations are *"merely recitations of the optimal workable ranges and do not impart patentability."*

Applicants respectfully disagree.

In fact, both Carli et al. and Dunn et al. teach away from the invention since:

in the one hand, they do not describe coated granules of microcrystals of ibuprofen;

in the other hand, they are directed to dosage forms in which the granules of active substance, for example ibuprofen, are formulated for a prolonged release, and not for immediate release as in the invention.

According to the present invention, "the ibuprofen preserves its physico-chemical integrity, the intrinsic

properties of the active ingredient being totally unchanged by granulation and coating" (see page 2 lines 28-30)

Due to the process used in Carli et al., the active ingredient which is loaded onto polymer particles "is in a thermodynamically active state, i.e. amorphous or as extremely small crystals (nanocrystals)" see column 2 lines 59-62.

Furthermore, it is specified in Carli et al. (see column 2 line 59) that the release time of the medicament present into the coated granules can be adjusted at will from a few hours to 24-48 hours.

And, it is interesting to note that example 10 in which ethylcellulose, hydroxypropylmethylcellulose and colloidal silica are used, results in a dissolution of 75% of the active substance in 420 min.

Dunn et al. teaches a controlled release tablet comprising an active ingredient, preferably aspirin, a release-controlling agent and an erosion-promoter.

Due to the process used in Dunn et al., the granules are matrix particles in which the active ingredients are homogeneously dispersed within the granules, without any coating layer which mask the active.

Furthermore, it is specified that the tablets including the granules of active substance are intended to provide delayed disintegration rates and prolonged dissolution times (see, column 3 lines 37-38).

It appears from the examples (see table 4) that complete dissolution of active substance is obtained after 300 minutes.

As indicated above, both documents teach with prolonged release of active substance, whereas, on the opposite, coated granules of ibuprofen according to the invention allow a substantially immediate release of ibuprofen when the particles reach the gastric medium.

In particular see example 1, where it is indicated that the dissolution time of granules of ibuprofen (200mg) is 30 min.

Consequently, both Carli et al. and Dunn et al. teach away from the invention.

The man skilled in the art could not use the teaching of said documents to obtain granules presenting a quick dissolution.

Even if he used said documents he would have never deduced the specific composition of the coated granules according invention which allows the obtention of a quick dissolution , good palatability properties while preserving the physico-chemical integrity of the ibuprofen microcrystals.

Said composition can no more be deduced from Ghanta et al. which describes ibuprofen which is encapsulated by coacervation process, and not coated, with a composition based on cellulose acetate phthalate and gelatin.

Claims 10 is thus inventive over Carli et al. and Dunn et al. in view of Ghanta et al..

Claims 11 to 16 which depend on claim 10 are also inventive.

Incidently, Applicants respectfully stress on the fact that Dunn et al. does not teach the addition of an alkaline compound in the granule itself. The pH conditions of 7.5 are the one set for dissolution testing according to USP XX (see examples 16-23).

On the opposite, in the present specification, it is specified that "an alkali metal salt of an organic origin" can be used to enhance the solubilization of ibuprofen when dissolving in the gastro-enteric fluids, by creating an alkaline micro-pH.

Claim 17 relates to a process for preparing coated granules according to claim 10.

The process for preparing coated granules of ibuprofen microcrystals cannot be deduced from Carli et al., or Dunn et al. in view of Ghanta et al.

According to Carli et al., the granules are prepared with a process comprising two steps. In a first step, the active ingredient is loaded onto a polymer which is insoluble but swellable in water (see column 2 lines 68-69) and in the second step, the obtained polymer particles loaded with the active ingredient, are coated with a polymer or enlarged to granules using for example a wet-granulation process.

Due to the first step, which is carried out by dissolution of the active in a solvent (see column 2 line 3), co-grinding (see column 2 line 25) or co-heating the active ingredient and the polymer (see column 2 line 46), the

physico-chemical integrity of the microcrystals of ibuprofen cannot be preserved.

According to Dunn et al., the active ingredient is intimately mixed with the erosion-promoting agent, then a solution of the release-controlling agent is added to form a wet granular mass. There is no coating step of the obtained matrix particles.

Ghanta et al. teaches a method for microencapsulating a water-insoluble NSAID medicament with cellulose acetate phthalate and gelatin microencapsulating material.

The method used in Ghanta et al., is a coacervation process in which gelatin is used as a hardening agent of the core shell (see column 3 lines 3-21).

It is clear that a man skilled in the art would not combine said process with the process according to Dunn et al. or Carli et al.

Even if he combines said documents, he would never obtain the process according to the invention, since it is impossible to use a process according to Ghanta to obtain particles which are coated with a coating composition comprising silica, hydroxypropylmethylcellulose and ethylcellulose, since none of them are hardening agents.

Claim 17 is thus inventive. Claims 18 to 22, which depend on claim 17, are also inventive.

In view of the above, it is considered that the application is now in proper form for allowance.

Favorable consideration and prompt allowance of these claims are respectfully requested.

Respectfully submitted.

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

March 18, 2003

By: Allan H. Fried

Allan H. Fried
Reg. No. 31,253
Seven Penn Center, 12th Floor
1635 Market Street
Philadelphia, PA 19103-2212
(215) 567-2010
Attorney for Applicants